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10/586,894	07/21/2006	Francis Sean Moolman	ADADA4.001APC	5369

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EXAMINER	
KOSSON, ROSANNE	
ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/586,894	MOOLMAN ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23,30 and 31* is/are pending in the application.

4a) Of the above claim(s) *3,18,22 and 23* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,11-17,20,21,30 and 31* is/are rejected.

7)☒ Claim(s) *10 and 19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group 1, claims 1-21, 30 and 31, in the reply filed on March 30, 2009 is acknowledged. Applicants' elections of the species of porous particles (claim 2), water-in-oil emulsion (claim 8) and an oil as the hydrophobic phase (claim 16) are also acknowledged. Applicants have not indicated whether the species elections are with traverse or without traverse. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the species elections have been treated as an election without traverse (MPEP § 818.03(a)). Claim 1 has been amended. Claims 24-29 have been canceled. No claims have been added. Claims 3, 18, 22 and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Accordingly claims 1, 2, 4-17, 19-21, 30 and 31 are examined on the merits herewith.

Regarding claim 23, Applicants' election of the species of pH as the modified parameter is acknowledged. But, as discussed above, this claim is withdrawn, as it is part of Group 3.

Regarding the restriction of Groups 1-3, in their traversal, Applicants assert that there is unity of invention, because Clark, Jr. does not disclose the common technical feature. In reply, as previously discussed, Clark, Jr. does disclose the common technical feature, enzyme particles made by cross-linking the enzyme molecules contained in droplets in an emulsion. Clark, Jr. refers to this preparation as a gel, while Applicants refer to their preparation as hollow, spherical particles. But, the two are the same, because they are made by the same method. The claim language is broad, and, as recited in the claims, the claimed particles are those of Clark, Jr. Clark, Jr. describes his composition macroscopically, while Applicants describe the

structure of each particle. But, this aspect does not distinguish the two. In view of the foregoing, the restriction requirement is deemed proper and is made final.

Claim Objections

Claims 1, 2, 4-17, 19-21, 30 and 31 are objected to because of the following informalities. Claim 1 recites the term "internally or externally," but it is not clear whether Applicants are referring to the inside and outside of the enzyme or the particle or the droplet. Also, for clarity, the portion "which are stable and in which the enzymes are immobilized .. sites of the enzymes being oriented" should read "which are stable and in which the enzyme molecules are immobilized … sites of the enzyme molecules being oriented." Clarification and appropriate correction are required.

Claim 7 and its dependent claims (8-17, 19, 30 and 31) are objected to because of the following informality. The claims recite the abbreviations O phase, W phase, O/W emulsion and W/O emulsion. O appears to mean oil and W appears to mean water. These terms should be written out in full, at least the first time that they are used, with the abbreviations following in parentheses, if they are used. The meaning of the claims should be clear. Appropriate correction is required.

Claim 12 is objected to as not further limiting claim 7, because claim 1, from which claim 7 depends, already recites the step of claim 12. Applicants may wish to cancel this claim.

Claim 10 should have commas added as follows. The term “occupation of or reaction with the active sites” should read “occupation of, or reaction with, the active sites …”

In claim 16, the listed items should be separated by commas and not semicolons.

Claim 19 recites the term "HLB." This term should be written out in full with the abbreviation following in parentheses, if desired, so that the meaning of the claim will be clear.

This term appears to mean "hydrophilic-lipophilic balance." Also, for clearer claim language, claim 19 could be rewritten to recite “the process according to claim 7 … wherein said process comprises, prior to cross-linking, (1) the formation of an initial emulsion in which hydrophobic phase droplets are dispersed in a continuous hydrophilic phase, (2) centrifugation of the emulsion and separation of a concentrated emulsion from a dilute hydrophilic phase to increase lipase purity, and (3) the inversion of the emulsion to form an emulsion in which hydrophilic phase droplets are dispersed in a continuous hydrophobic phase by the addition of a surfactant with a lower hydrophilic-lipophilic balance (HLB) value." Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 17, 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 20 recite the term "modifier." This term is not defined in the specification. A few examples are provided: amino acids, amino compounds, proteins, long-chain hydrocarbon aldehydes, other modifiers which bind covalently or otherwise to enzymes, a surfactant, a precipitator and an additive. But some of these items are vague as well, such as a precipitator, an additive, something that binds in any fashion to an enzyme, and an amino compound that is not a protein or amino acid. Clarification of what modifier means and appropriate correction are required. The term may be replaced with more definite claim language.

Claim 17 recites the term "mediator." This term is not defined in the specification, and its meaning is unclear. One example of a reaction mediator is provided, something that is suitable for regenerating a second redox enzyme when the emulsion droplets contain two redox enzymes. But, it cannot be determined if a reaction mediator and a mediator are the same thing or two different things. Even for Applicant's example, it cannot be determined if the thing that is suitable is a composition or a molecule or an object that is used in a method step.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 7-9, 11-17, 20 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Goldberg et al. (US 4,671,954). Goldberg et al. disclose a method of making a composition that is recovered from the liquid phases from which it is made, as it is a controlled-release drug delivery vehicle. The composition is a W/O (water-in-oil) emulsion comprising porous particles. The composition is made by making an aqueous solution of a protein or polypeptide, such as an enzyme, and dispersing the water phase in the oil phase with the aid of one or more modifiers. Any suitable protein or polypeptide, such as an enzyme, may be used in this method. A modifier, such as polyglutamic acid, is an amino acid that may be used in this method. It is a modifier that modifies (reduces) the hydrophobicity and increases the hydrophilicity and the surface charge of the particles. Increased surface charge, with each particle having the same negative surface charge, reduces the aggregation of the particles. The hydrophilic phase comprises water mixed with, i.a., polyethylene glycol, a dispersion-stabilizing

polymer, in the form of a block copolymer of polyethylene glycol and polypropylene glycol. The hydrophilic/aqueous phase may comprise additional molecules, polypeptides or macromolecules. Thus, the aqueous phase may comprise a second enzyme. The oil phase can be a hydrocarbon, such as toluene. This method includes the step of cross-linking the protein molecules in the microspheres with an agent such as glutaraldehyde. See col. 2, line 20, to col. 3, line 54; col. 4, lines 4-33; col. 5, lines 1-27; col. 11, lines 13-25 and col. 31, lines 17-35. The enzyme particles are recovered from the second liquid phase (see col. 6, lines 24-25). The first liquid phase (the aqueous phase) is extracted by drying the particles (see Examples 1, 21 and 25 in cols. 6, 15 and 16). The specification discloses that the step of extracting the aqueous phase is carried out in one of several ways, such as drying (see p. 5, last paragraph).

In view of the foregoing, a holding of anticipation is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-9, 11-17, 20, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldberg et al. (US 4,671,954), in view of Margolin et al. (WO 01/62280 A2). The teachings of Goldberg et al. are discussed above. Goldberg et al. do not disclose that the enzyme is a lipase or that the aqueous phase comprises a buffer.

Regarding using a lipase as the enzyme (claims 5-6), Margolin et al. disclose that lipases, as replacement therapy, are administered to patients suffering from disorders of fat malabsorption, such as chronic pancreatitis, other pancreatic diseases and cystic fibrosis. These patients suffer from, i.a., abdominal pain, essential fatty acid deficiencies and fat-soluble vitamin deficiencies (see p. 1). Margolin et al. disclose that a stable formulation of a lipase to treat these diseases is a cross-linked crystalline lipase, from an organism such as *Burkholderia cepacia* (see pp. 2-4) (an older name for which is *Pseudomonas cepacia*). The enzyme may be cross-linked with a variety of conventional cross-linking agents, such as glutaraldehyde (see pp. 5-6).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use a lipase, such as lipase from *Burkholderia cepacia*, in the method of Goldberg et al., because Goldberger et al. disclose that their method of making protein microspheres, as a drug-delivery formulation, can be practiced with any protein, including any enzyme, while Margolin et al. disclose that this lipase is a known therapeutic agent. Goldberg et al. disclose that stabilization of the enzyme is achieved by forming cross-linked particles. Margolin et al. disclose that stabilization is achieved by forming cross-linked crystals. But the artisan of ordinary skill would have had every expectation of success in using a *Pseudomonas* lipase in the method of Goldberger et al. as the cross-linked enzyme.

Regarding claim 30, it would have been obvious to one of ordinary skill in the art at the time of the invention to dissolve the enzyme in the method of Goldberg et al. in an aqueous buffer, rather than in water, because the artisan of ordinary skill would have known that a conventional buffer, such as PBS or Tris-HC, would have prolonged or maintained the activity of the enzyme by maintaining the pH and salt concentration around the enzyme. Therefore, this claim does not distinguish the invention over the prior art.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Abe et al. ("Surfactant-chymotrypsin complex as a novel biocatalyst in organic media," Journal of Fermentation and Bioengineering 83(6):555-560, 1997) in view of Goosen et al. (US 4,492,684).

Abe et al. disclose a method making an O/W emulsion of an enzyme, a method in which any water-soluble enzyme can be used. The emulsion is made by dissolving the enzyme in buffer, mixing it with an aqueous salt solution and a solution of a surfactant in a hydrophobic solvent, and homogenizing this mixture (see p. 556). The surfactants of Abe et al. are biologically compatible. Abe et al. disclose that O/W emulsions in which the enzyme was emulsified with a surfactant were known previously for lipases, but not for other enzymes. Abe et al. note that the purpose of the emulsion is to coat the enzyme to maintain its activity (see p. 555). Abe et al. do not disclose that the enzyme is cross-linked.

Goosen et al. disclose a method of making an O/W microbead emulsion of a protein mixture, albumin and insulin, by adding an aqueous suspension of albumin, insulin and glutaraldehyde to an oil phase and rapidly stirring the mixture to form the emulsion. The purpose of cross-linking the proteins is to form a slow-release composition, in which the insulin is released a controlled, gradual rate. A second purpose of the cross-linking is increase the shelf-life of the composition. It would have been obvious to one of ordinary skill in the art at the

time of the invention to use a cross-linking agent in the method of Abe et al., by adding it to the mixture in the homogenizer, because Goosen et al. disclose that, when proteins in an O/W emulsion are cross-linked, the proteins are released from the emulsified droplets at a controlled rate, and the emulsion is more stable. The artisan of ordinary skill would have known that any protein may be cross-linked by glutaraldehyde, whether or not the protein is an enzyme.

In view of the foregoing, a holding of obviousness is required.

Claims 10 and 19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The cited references do not provide the motivation to perform the steps recited in these claims, adding a protectant to the active site of the lipase and making the emulsion by inverting an O/W emulsion.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is (571)272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652
rk/2009-04-14

/Delia M. Ramirez/
Primary Examiner, Art Unit 1652